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Original article

Patients with axial spondyloarthritis report significant differences between men and women and high impact of the disease: Large websurvey analysis

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ABSTRACT

Objective: In axial spondyloarthritis (axSpA), mounting evidence shows female patients to experience a higher disease burden. These differences appear to be particularly large in South America. One explanation could be inequity in treatment access between men and women. The objective was to evaluate gender differences in disease burden and work participation, and the potential influence of treatment, in Latin American patients.

Methods: A cross sectional online survey among axSpA patients, collecting disease characteristics, treatment, disease burden (BASDAI, BASFI, ASAS Health Index) and work participation (WPAI). Associations between gender and disease burden or work participation were assessed through regression analyses, correcting for treatment.

Results: AxSpA was reported by 472 participants (63% women) and disease activity (BASDAI ≥ 4: 83%), ASASHI (≥ moderately impaired: 91%) and work disability (absenteeism: 41%; presenteeism 82%) were high. Biological use was very low (20%), while 34% used opiates. Females had significantly higher BASDAI, ASAS HI, work absenteeism and presenteeism, although were less likely to receive biologics (26% versus 16%, $P < 0.01$). Gender differences disappeared after correction for treatment.

Conclusions: This web survey in Latin American axSpA patients shows a high disease burden and work impairment. The use of biologics is low, while the use of opiates was alarmingly high. Women used significantly less biologics despite reporting a worse disease state and work disability, which could be due to treatment inequity.

1. Introduction

In axial spondyloarthritis (axSpA), mounting evidence shows important gender differences in disease characteristics and, importantly, disease burden [1]. Female patients suffer a longer diagnostic delay, higher disease activity and less efficacy of biologic treatment. A recent study reported differences in disease activity to be particularly larger in South America [2].

In general, the availability of biologics across the globe remains unequal [3]. In Chile, patients with ankylosing spondylitis (AS) in the public health system do not have guaranteed access to expensive biologics, unless self-financed. Consequently, many patients cannot work, and receive a disability pension from the government [4]. This is important, since a lower socio economic status is associated with a higher disease burden, whereas biologic use enhances work participation [2,5]. A large study in Brazilian axSpA patients showed a lower use of biologics (and NSAIDs) in female patients, which could (partly) explain both the higher disease burden and work disability in this group [6]. However, studies on gender differences in disease burden, treatment and work participation in Latin American axSpA patients are scarce.

The main objective of this large websurvey was to obtain insight into gender differences in disease burden and work participation, and the potential influence of treatment, in Latin American (Chilean) patients with axSpA.

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2. Methods

2.1. Study population and design

A cross sectional online survey was conducted in Chile among participants aged ≥ 18 years who reported to be diagnosed with spondyloarthritis (SpA) (any type). For this study, only patients with an axSpA diagnosis were selected. Patients were recruited via the internet website of the Chilean Spondyloarthritis Patient Foundation ("Espondilitis Chile"), associated social media (Twitter, Facebook) and Google AdWords (targeted advertisement, search terms: arthritis, spondyloarthritis and ankylosing spondylitis, in Spanish). Reminders were sent once every week (July–September 2018). Duplicates were removed manually by identifying participants that reported the same age, first letters of first- and surname and the timing of survey participation. Participation was voluntarily and without financial incentives. Full local ethical approval was obtained from the medical ethics committee (number 2018-47) of the Clínica Alemana-Universidad del Desarrollo medicine faculty in Santiago, Chile. Research was carried out according to all ethical standards, including the Helsinki Declaration. Consent was requested before entering the questionnaire, after informing on the survey purpose.

2.2. The survey

The survey was written in the local language: Chilean Spanish. Information was requested mostly via multiple-choice options and, in some occasions, requesting a number (age, year, amount of hours). Patients were asked about their diagnosis, providing the options: radiographic (r-)axSpA/ankylosing spondylitis, non-radiographic (nr-)axSpA, psoriatric arthritis, reactive arthritis, IBD-associated SpA, juvenile SpA, other type of SpA. The current use of any biological agent was assessed via a multiple-choice question ("yes", "no", "unsure"). Additionally, information was requested on demographics (gender, age, ethnic background), disease characteristics (age at symptom onset, age at diagnosis, HLA-B27 status) and current concomitant treatment (NSAIDs, DMARDs and opiates).

The disease activity, physical functioning and quality of life were assessed by the Spanish (validated) versions of the Bath AS disease activity index (BASDAI), Bath AS functional index (BASFI) and ASAS health index (ASAS HI) [7–9].

Work status was evaluated through the work productivity and activity impairment (WPAI) questionnaire, with the subdomains absenteeism (% work time lost), presenteeism (% productivity loss at work), work impairment (combination of absenteeism and presenteeism) and activity impairment (percentage activity loss), in the last seven days, due to back pain. WPAI scores were only applicable to men < 65 years and women < 60 years (working-age Chile). Absenteeism, presenteeism and overall work impairment did only apply to employed participants.

2.3. Patient involvement

The axSpA patient foundation (Espondilitis Chile) was fundamentally involved in the study aim and evaluation of the survey, feasibility and patient perspective, through meetings between the investigator and foundation board and a pilot session. The foundation played an essential role in patient recruitment, through their social networks.

2.4. Statistical analyses

Data are presented as mean (± standard deviation, SD), median (with first and third quartile, Q1–Q3), number (with percentage) or percentage (with 95% confidence interval, CI). Dichotomous values were compared with the Chi square test, and for parametric continuous variables linear regression analysis was used. Parameters without a normal distribution, also after log transformation, were analyzed with the Mann-Whitney *U* test.

The BASDAI was reported as a continuous value and dichotomized into high (BASDAI ≥ 4) and low (< 4) disease activity. The ASAS health index sum score was categorized into no (≤ 5.0), moderate (> 5.0 to ≤ 11.9) and severe impairment of functioning (≥ 12.0). WPAI final scores were presented as the number of patients with any impairment (> 0% versus 0%), and the mean or median level (%) of impairment for the patients with any impairment.

The association between gender (independent variable) and BASDAI (continuous), BASFI (continuous), ASAS HI (binary: severe versus moderate or no impairment), absenteeism (yes/no) or presenteeism (yes/no), was first assessed through univariable linear or logistic regression analyses. If significant gender differences existed within the overall BASDAI, BASFI or ASAS HI scores, exploratorily, the individual questions of these items were assessed for gender differences as well. Next, multivariable regression analyses were performed, with stepwise correction for age and disease duration (step 1), biologic (step 2), NSAIDs (step 3) and opiates (step 4). Secondarily, effect modification by biologic use on the association between gender and the aforementioned disease parameters was evaluated by including a cross-product interaction term (biologic*gender) as independent variable in the multivariable regression models. For parameters with an interaction term of $P \leq 0.10$, subgroups were further explored. All statistical analyses were performed using IBM SPSS statistics for Windows, V.22 (IBM Corp).

3. Results

3.1. Study population

Between 6th of July 2018 and 7th of October 2018, 625 patients completed the survey, six duplicates where removed and 472 were included because of reporting a diagnosis of axSpA. Of the 472 patients, 63% were female (Table 1).

3.2. Gender differences in disease burden

The mean BASDAI and BASFI scores were high and the majority reported a high disease activity (83%, Table 1). Furthermore, 91% had an impaired level of functioning (ASAS HI score). Only 20% of the patients reported current use of a biologic, while the number of patients on NSAIDs was fairly higher (78%) and 34% used opiates.

Women reported a significantly higher disease activity (BASDAI), compared to men (6.3 [SD2.0] versus 5.8 [SD2.3], $P = 0.03$, Table 1), scoring particularly worse on the level of fatigue and tenderness (Fig. 1). Furthermore, women were more impaired in daily life (ASAS HI score), which applied to almost all ASAS HI domains (Fig. 1). In addition, 96% of the women was moderately or severely impaired, compared to 80% in men ($P < 0.01$, Table 1). The overall BASFI score did not differ significantly between men and women.

3.3. Gender differences in work participation

Only 64% of the patients reported to have a paid job and absenteeism was mentioned by 41% of the employed patients (Table 1). Of the employed patients that did work in the last seven days ($n = 255$), 77% reported presenteeism (Table 1).

Women were less likely to have a paid job than men. Women with a job were significantly more likely to miss work hours due to their disease, compared to men, or to experience presenteeism

Table 1
Patient characteristics, disease burden and work participation.

	Overall (*n* = 472)	Men (*n* = 173)	Women (*n* = 299)	p
Gender, no. of males (%)	173 (37)			
Age, mean yrs (SD)	42 (10)	43 (11)	41 (9)	0.02
Age at diagnosis, mean yrs (SD)	35 (10)	34 (11)	35 (9)	ns
Age onset symptoms, mean yrs (SD)	28 (10)	28 (11)	28 (10)	ns
Diagnostic delay, median yrs (IQR)	4 (1, 10)	3 (1, 10)	5 (1, 11)	ns
Disease duration, mean yrs (SD)	13 (10)	13 (9)	15 (12)	0.02
HLA-B27 positive[a], *n* (%)	232 (49)	110 (64)	121 (40)	< 0.01
Current treatment, *n* (%)				
DMARD	261 (55)	88 (51)	173 (59)	ns
NSAIDs	370 (78)	126 (73)	244 (82)	0.02
Biological	92 (20)	45 (26)	47 (16)	< 0.01
Opiates	158 (34)	43 (25)	115 (39)	< 0.01
Disease burden parameters				
Patient global disease, nrs, mean (SD)	6 (3)	6 (3)	6 (2)	ns
BASDAI, nrs, mean (SD)	6.1 (2.1)	5.8 (2.3)	6.3 (2.0)	0.03
BASDAS ≥ 4, *n* (%)	390 (83)	131 (76)	258(86)	< 0.01
BASFI, nrs, mean (SD)	5 (3)	5.1 (2.8)	5.4 (2.4)	ns
ASAS Health Index, *n* (%)	10 (4)	9 (4)	10 (3)	< 0.01
Normal[b]	44 (9)	24(19)	10(4)	
Moderate impaired[b]	267 (57)	60(48)	138 (56)	< 0.01
Severely impaire[b]	161 (34)	40(32)	99 (40)	
Work participation[c]				
Currently paid job[c], *n* (%)	295 (65)	127 (77)	168 (58)	< 0.01
Absenteeism[d], *n* (%)	122 (41)	41 (32)	81 (48)	< 0.01
Absenteeism[e], % time, median (IQR)	31 (10, 100)	40 (12, 100)	25 (8, 100)	0.31
Presenteeism[d,h], *n* (%)	196 (77)	78 (70)	118 (82)	< 0.01
Presenteeism[f], % time, mean (SD)	46 (26)	42 (27)	49 (25)	0.10
Overall work impairment[d], *n* (%)	237 (80)	95 (75)	142 (85)	0.01
Work impairment[g], % time, median (IQR)	56 (30, 88)	50 (20, 83)	60 (37, 90)	0.09
Overall activity impairment, *n* (%)[c]	424 (93)	144 (87)	280 (97)	< 0.01
Activity impairment, % time, mean (SD)[c]	59 (27)	57 (29)	59 (26)	0.41

ASAS HI: ASAS Health Index; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; DMARD: disease modifying anti-rheumatic drug; NSAIDs: nonsteroidal anti-inflammatory drugs; SpA: spondyloarthritis.

[a] HLA-B27 unknown in 94 patients (30 men, 65 women).

[b] normal functioning (ASAS HI ≤ 5.0), moderate impairment (> 5.0 to ≤ 11.9), severe impairment (≥ 12.0).

[c] In all patients of working-age (166 men, 291 women).

[d] Amongst patients with a job.

[e] % of work time lost, if absenteeism.

[f] % of work time with less productivity, if presenteeism.

[g] % of work time with less productivity (due to absenteeism or presenteeism), if work impairment.

[h] Only for patients that were not 100% absent (*n* = 255; 11 men, 144 women).

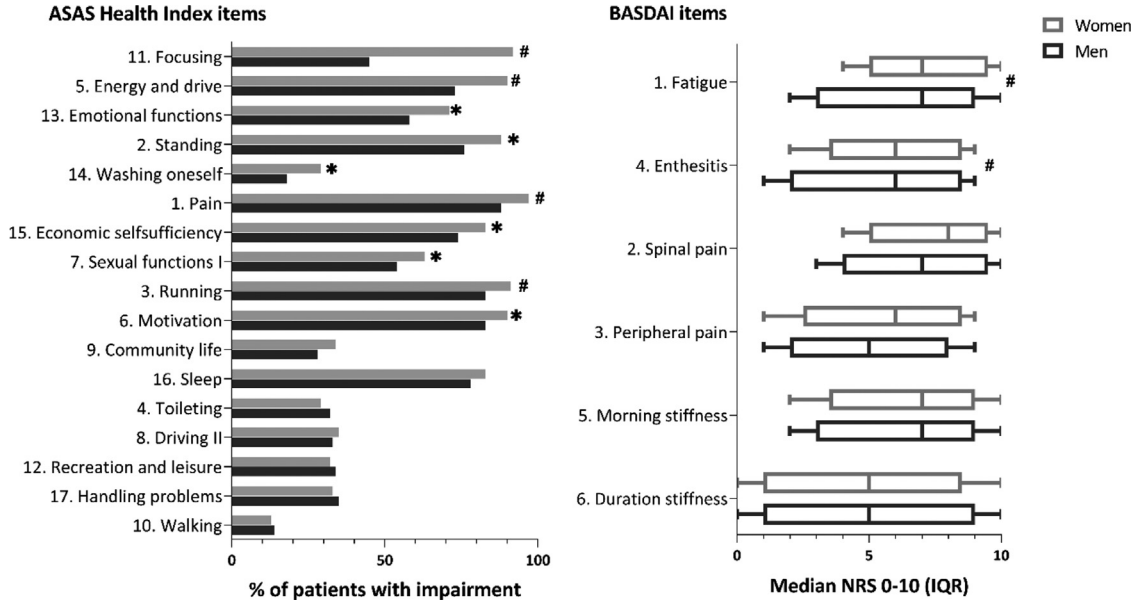

Fig. 1. Gender differences in BASDAI and ASAS Health Index items. Values are depicted as percentage of patients answering "yes" to the individual ASAS HI items on impairments in daily life, or as the median NRS score (BASDAI, with interquartile range, p10 and p90). I, not applicable in 16 men and 41 women; II, not applicable in 44 men and 113 women; *, $P < 0.05$; ** $P < 0.01$.

Table 2
Gender differences in disease burden and work participation (female versus male patients).

	BASDAI			BASFI			(ASAS HI)[b]			Work absenteeism			Work presenteeism		
	β	95% CI	p	β	95% CI	p	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p
Gender, crude	0.5	0.1–0.9	0.02	0.4	−0.1–1.0	0.11	1.7	1.1–2.6	0.02	2.0	1.2–3.3	<0.01	2.3	1.1–4.6	0.02
Adjusted for[a]															
1. age, disease duration	0.5	0.1–0.9	0.02	0.6	0.1–1.1	0.02	1.8	1.2–2.8	0.01	2.1	1.3–3.5	<0.01	2.5	1.2–5.0	0.01
2. +biologics use	0.4	−0.1–0.8	0.07	0.5	0.02–1.0	0.05	1.7	1.1–2.6	0.03	2.0	1.2–3.4	0.01	2.4	1.2–5.0	0.02
3. +NSAIDs use	0.3	−0.1–0.8	0.12	0.4	−0.1–0.9	0.10	1.6	1.0–2.5	0.05	1.9	1.1–3.2	0.02	2.3	1.1–4.8	0.03
4. +opiates use	0.2	−0.3–0.6	0.46	0.2	−0.3–0.7	0.41	1.3	0.8–2.2	0.22	1.5	0.9–2.7	0.12	§		

Female versus male patients. §: additional correction for opiates was not performed because 100% of the patients with opiate treatment reported presenteeism. B: linear regression coefficient; CI: confidence interval; ns: non-significant; OR: odds ratio; *P*, *P*-value.

[a] Adjusted analyses were depicted with stepwise addition of variables (with step 4 containing both age, disease duration, biologics, NSAIDs and opiates)

[b] Severe daily impairment (ASAS HI sum score ≥ 12) versus no or moderate impairment (ASAS HI sum score < 12)

(Table 1 and 2). Also, women reported more often to have experienced financial changes due to their disease (ASAS HI question 15; 83% of the women, 74% of the men, $P = 0.02$, Fig. 1).

3.4. Biologic treatment and gender differences

3.4.1. Biologic treatment

Patients with a biologic had less NSAIDs (65% versus 82%, $P < 0.01$), significantly lower BASDAI (5.2 (SD2.2) versus 6.3 (SD2.1), $P < 0.01$) and BASFI (4.7 (SD2.4) versus 5.5 (SD2.6), $P < 0.01$) scores and had a lower chance of severe impairment in daily life (ASAS HI ≥ 12; 22% versus 37%, $P = 0.02$), compared to non-users. In addition, biologics were associated with a higher chance of a paid job (76% versus 62%, $P = 0.01$) and a lower risk of being absent from work (31% versus 45%, $P = 0.04$).

3.4.2. Gender differences and the influence of biologic treatment

Although women reported a worse disease state, biologics were used significantly more often in men (26%, 95% CI [20;33], versus 16% 95% CI [12;20], $P < 0.01$), and this was not significantly different for patients with- and without a paid job (data not shown). In contrast, women were more likely to use opiates and NSAIDs (Table 1). Importantly, in multivariable analyses, the association between gender and BASDAI and BASFI disappeared after correction for biologics, whereas the association with absenteeism disappeared after correction for opiates (Table 2).

Next, we evaluated whether gender differences were different for patients with and without biologics. Biologic-use was only an effect modifier for the association between gender and BASDAI ($P = 0.08$). After stratification, men and women with a biological did not differ significantly in disease activity (BASDAI, BASDAI≥4), nor the use of NSAIDs or DMARDs, but female patients used opiates more often (74% versus 55%, $P = 0.01$).

In contrast, in patients without a biological, women showed a significantly higher BASDAI (6.5 ± SD1.8 versus 6.0 ± 2.4 in men, $P = 0.02$; BASDAI ≥ 4 in 90% versus 77%, $P < 0.01$), compared to men without a biologic. Interestingly, these women did not use more co-medication (NSAIDs, DMARDs), but used slightly more opiates (39% versus 28%, $P = 0.05$).

4. Discussion

This large web survey is the first to be performed in axSpA patients in Latin America and showed that women generally experienced a higher disease activity and more impairment in daily life and work participation, compared to men, regardless of age and disease duration.

The fact that women reported a worse disease state is in accordance with earlier studies and seems to be a problem particularly in South America [1,2]. Importantly, in this study women were less likely to use biologics compared to men, and this was the same for patients with and without a job. Interestingly, gender differences in disease activity and physical functioning disappeared after correction for biologic-use. This indicates that the worse disease state that was found in women is (partly) caused by lower access to adequate treatment (biologics). Furthermore, among the patients without biologics, women did not receive more co-medication while reporting a higher disease activity. This adds to the suggestion of an important inequality in treatment access, regardless of work participation, between men and women. This gender difference in biologic use has been reported before both in global studies and for other rheumatic diseases [3,10]. An explanation could be that the symptoms of axial disease are under-recognized in women.

Gender differences in the specific items of the BASDAI and BASFI have only been reported scarcely. In an explorative analysis, the current study found a higher level of fatigue (BASDAI 1) and enthesitis (BASDAI 4) in women. This was also found in other study, that included recently diagnosed patients, although it also reported more spinal and/or peripheral pain [11]. Last, to our knowledge, no other study reported gender differences in the specific ASAS HI items.

This study found a relatively high level of disease burden and daily impairment, compared to a recent population study in 22 countries around the world, but also the iberoamerican RESPONDIA cohort [12,13]. In addition, the overall employment state in this study was lower than reported by a recent global study, and also than the national prevalence in the corresponding age groups in the general population (Chile 2017: of women and men between 25–60 years of age, respectively 60–65% and 85–88% were employed) [14,15]. The high prevalence of opiates use, especially in women, is alarming in the perspective of the increasing global problems with opioid use, addiction and side effects, and the lack of effect on inflammatory processes.

One explanation for the relatively poor disease state is the very low use of biologics (20%), which was lower than the 40% reported for other South American countries [16]. It is unclear whether people without biologics were more likely to respond. However, the national use of biologics is unknown but might be rather low since 70% of the Chileans receive care in the public sector (low access to biologics) and Chile has a very low population density, with patients in sparsely populated areas having very limited access to specialized care in general. Another explanation might be a lower level of social desirability when disease burden is assessed trough an internet survey, since a recent web study in European and Russian patients found a similar level of impairment in daily- and working life [17]. By all means, these results may reflect an important lack of access to adequate treatment options in Chile.

For the conduction of this survey, a web platform (google documents) was used, easily accessible via computer or smartphone, applying internationally accepted and widely used questionnaires for axSpA. As for axSpA, so far, web surveys have only been used

very limited to perform research and, to our knowledge, this is the first to be conducted in Latin America. Online surveys have the advantage of facilitating data collection, a high response rate, and the lack of social desirability bias. In particular in countries with relatively low population densities and inequalities in treatment, conducting research via internet surveys can become an increasingly important method to obtain a more true image of the overall disease burden. The evaluation of axSpA through internet surveys correlates well with paper surveys and self-assessment with tablet- or smartphones is increasingly incorporated into clinical practice [18].

This study has a few limitations. First, web surveys induce a risk of selection bias, with specific groups being more likely to respond or being unreachable. The proportion of women in this study was higher than expected in an axSpA population. This is probably caused by the fact that women are more likely to respond to web surveys, which was seen in previous studies in axSpA as well [19,20]. Also, the level of disease burden was remarkably high and one could argue whether these patients were more interested in survey participation. Secondly, patient inclusion was based on a self-reported axSpA diagnosis, without the possibility to verify. However, axSpA is a rather specific diagnosis and participants reported their diagnosis via a multiple-choice question, with many options, including 'other'. Third, the cross sectional design hampers the identification of specific causes for the gender differences found in this study. Lastly, in this study, after correction for NSAIDs use, the associations between gender, and the ASAS HI was lost, while the use of NSAIDs was significantly higher in women. This could be caused by the overall high number of NSAIDs- and low number of biologic users resulting in a loss of statistical power.

In conclusion, this is the first large web survey on axSpA patients in Latin America, and one of the few studies to describe gender differences in disease burden and work participation on this continent. Despite reporting a high disease burden and high work disabilities, only a minority of the patients mentioned to receive adequate treatment with biologics. This suggests an imperative need to improve access to care, and the alarmingly high prevalence of opiate use further substantiates this lack of adequate treatment. Furthermore, although women experienced a higher disease burden and work disability, they were less likely to use biologics, which suggests an important treatment inequality between men and women.

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Disclosure of interest

The authors declare that they have no competing interest.

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